DETAILED ACTION

Examination of the instant application has been transferred to Examiner Valarie Bertoglio, AU 1632.

Applicant's election with traverse of Group IV, claims 48-66 in the reply filed on 03/06/2008 is acknowledged. The traversal is on the ground(s) that the structure of the nucleic acid of Group III and the transgenic animal of Group IV are closely interrelated and that they are related as intermediate and final product. This argument is not persuasive. While the nucleic acid of Group III is used in making the animal of Group IV, it is held that the nucleic acid is not an intermediate in the sense exemplified by Applicant at page 8 of the election. The animal is not merely an extension or modification of a nucleic acid intermediate. The nucleic acid is a reagent that is used in making the claimed animal. The nucleic acid has many uses and is useful outside the scope of the animal and is, in this sense, a final product itself. The novelty of the animal would not be indicative of novelty of the nucleic acid. The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claim 57 is objected to because of the following informalities: Line 11 of claim 57 recites '(v) (v)'. Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a transgenic mouse whose genome comprises a nucleic acid

comprising a FSHβ-LCR operably linked to a gene encoding a ligand-controllable receptor and separately encoding a Tet operator and minimal promoter operably linked to a gene encoding FSHβ, said method comprising, introducing said nucleic acid in to a mouse fertilized oocyte, implanting said fertilized oocyte into a pseudopregnant female host, obtaining a chimeric offspring from said host and mating the chimera to obtain a transgenic mouse whose genome comprises and expressed the nucleic acid wherein female mice exhibit increased ovulation does not reasonably provide enablement for the claimed method using 1) any nucleic acid other than that recited above or 2) for any species of animal other mouse, or 3)for any phenotype other than increased ovulation or 4) for chimeric animals as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claim 48 is drawn to a method of making any species of transgenic non-human animal comprising a nucleic acid comprising 1) a response element operatively linked to a nucleic acid encoding ovine FSHβ and 2) a FSHβ promoter operatively linked to a FSHβ LCR and operatively linked to a nucleic acid encoding a ligand-controllable receptor wherein said receptor binds to the response element in the presence of a ligand. Claim 53 is drawn to a transgenic non- human animal comprising cells that contain said nucleic acid and wherein said animal produces increased numbers of gametes. Claim 57 is

drawn to a method of using the animal to enhance the production of gametes by administering a ligand for the ligand-controllable receptor.

The claims are broad in a number of respects. 1) The claims encompass use of a transgene comprising a response element operably linked to a nucleic acid encoding FSHβ without a minimal promoter. 2) The claims encompass any species of non-human animal. 3) The claims encompass increasing gamete number in both male and female animals. 4) The claims encompass chimeric animals rather than being limited to the germline transgenic animals discussed in the specification.

The specification has disclosed making a transgenic mouse whose genome comprises a nucleic acid as outlined in Figure 1. The nucleic acid has two distinct gene units. There is a FSHβ LCR and promoter operatively linked to a gene encoding a Tet receptor. Further downstream, physically linked but not operably linked, is a tet operator and a minimal promoter (page 19, paragraph 3) operatively linked to a gene encoding FSHβ. The specification discloses that the resulting transgenic mice, when administered the ligand (doxycycline) exhibit increased ovulation (page 32, paragraph 3).

There are general unpredictabilities of phenotype resulting from expression of a transgene in any species of animal. The source of these generic unpredictabilities include copy number, promoter strength, position effect and genetic background (for example, see Niemann, 1998, **Transg. Res**. 7, pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4 and Cameron, 1997, **Molec. Biol**. 7: 253-265, specifically page 256, lines 3-9; Matthaei, 2007, **J Physiol**, 582.2:481-488). Thus, one cannot predict, a priori, what effect any given transgene will have upon an animal.

More specifically, with respect to the instant invention, Kumar (1992, IDS) discusses how interspecies FSH heterodimers, as would be formed in the instant invention, may be glycosylated differently and such an occurrence would not ensure biological activity. Thus, it is not clear, in instances where a heterologous FSHβ is expressed, that a functional heterodimer forms. Accordingly, Kumar did not find that overexpression of human FSH–β in transgenic mice affected ovulation at all. Likewise,

McTavish *et al (***Endocrinology,** 2007, 148:4432-4439) discuss that transgenic overexpression of human FSHβ in mice leads to increased litter size in younger mice but decreased litter size in older mice. Thus, the art shows a number of bases of unpredictability of overexpression of FSHβ in transgenic mice.

The construct used by Kumar differs from that of the instant invention. While Kumar did show gonadotrope-specific expression of human FSH-β in mice, the regulatory region of the transgene included endogenous human FSHβ elements. Kumar did not observe any gametic phenotype in the resulting mice despite higher FSH levels. Kumar observed increased testicular weight in male mice and higher testosterone levels, however, litter sizes from the transgenic mice were no different from wildtype. The instant specification differs from Kumar in that it teaches use of a gonadotrope-specific inducible switch with a minimal promoter, such as the CMV-IE promoter to lead to increased ovulation. The specification fails to teach any other phenotype.

Thus, it would be unpredictable what phenotype any other transgene encoding any FSHβ other than ovine FSHβ would have in any species other than mouse. The interspecies heterodimer glycosylation states and respective activities have not been shown. The specification has shown only that ovine FSHβ heterodimers that form in mice have activity to lead to increased ovulation in females. No other construct has been shown and the ovine FSHβ construct has not been shown to lead to any other phenotype.

The claims encompass use of a FSHβ gene operably linked to a response element (such as a tet operator) without a minimal promoter. However, the specification has established that a minimal promoter is necessary for expression of the linked transgene (see page 19, paragraph 3). Thus, one of skill in the art would not know how to use the claimed invention without the presence of a minimal promoter because no FSHβ would be expressed from the transgene.

The claims also encompass chimeric animals wherein not all cells of the animal comprise the transgene. For example, claim 48 requires raising the founder animal, which would be chimeric to some

degree and, depending on the degree of chimerism in the gonadotropes, the required phenotype may not be obtained. Furthermore, claim 53 encompasses animals having any number of cells, including 2 cells of any type, that comprise the claimed nucleic acid construct wherein the animals produced higher levels of FSHβ and gametes. The specification is enabling for increased ovulation in non-chimeric mice whose genome comprises the above set-forth transgene wherein gonadotrope-specific expression is observed.

In light of the unpredictabilities set forth above, the method of enhancing the production of gametes of claims 57-66 should be limited to increasing ovulation with use of the above set forth construct. Increased spermatogenesis is not supported in the specification or the art at the time of filing. On the contrary, overexpression of human FSHβ fails to alter male gametogenesis (see Kumar, IDS).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Valarie Bertoglio, Ph.D./
Primary Examiner
Art Unit 1632